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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILLIAMS, LEONARD M	
ART UNIT	**PAPER NUMBER**
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/694,934	NCHEKWUBE ET AL.	
	Examiner	Art Unit	
	Leonard M. Williams	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10 and 12-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-10 and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Response to Amendments/Arguments

Claims 3 and 11 have been cancelled. No amendments have been made to the claims. Claims 1-2, 4-10 and 12-15 are pending.

Applicant's arguments filed 06/28/2007 have been fully considered but they are not persuasive. The applicant's have included a declaration with several references and a table where data is presented for four human subjects taking the dried leaf powder of the application over a period of 5 years. The applicant's provide only one data point for each year (except for subject 1 which only includes 3 data points). The applicant's assert that this data supports the conjecture that the claims as written are enabled and allowable. The examiner respectfully disagrees. The data in the table does not overcome the enablement rejection. The data presented shows four human subjects treated with the dried leaf powder and not the particular compounds claimed. Further the lack of data within a shorter period of time (less than a year) and without stating if the subjects have changed any other hyperlipidemia factors (exercise, additional medications, diet) makes the data insufficient to support that it is the dried leaf powder (much less any particular compound contained within) that is resulting in the lower triglyceride levels. Further the applicant's have asserted that animal examples are sufficient to provide enablement for the claims in humans. The examiner respectfully points out that the use of animal studies and the subsequent extrapolating of the animal

studies data to humans is done on a case-by-case basis. In some instances animal studies (models) provide clear and convincing evidence for human activity (toxicity). In many cases animal models fail to demonstrate positively or negatively the actions of a drug in humans. In the instant case the data in question comes from a single dog and is based on the administration of a particular compound (not the dried leaf powder of the human subjects). As such not only is the species different (dog vs. human) the compounds administered are different. There is no reason to expect a pure compound reacting in a dog to be sufficient to provide enablement for the administration of dried leaf powder to humans much less the compound itself to humans.

For the reasons stated above and for the reasons of record the rejections of the last office action are maintained. The rejections of the last office action are reproduced below.

This action is made **final.**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4-10 and 12-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the ad; (4) the predictability or unpredictability of the ad; (5) the breadth of the claims', (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The Nature of the Invention:

The rejected claims are drawn to "A method of treating a host having hyperlipidemia comprising administering to the host an effective amount of a compound having the formula...".

(2) Breadth of the Claims:

The breadth of the claims are exceptionally broad encompassing any method of treating a host having hyperlipidemia comprising administering to the host an effective amount of a compound having the formula...". There are no limitations as to other

ingredients as the claim language is open and any type of hyperlipidemia is encompassed in the method of treatment.

(3) Guidance of the Specification:

The guidance of the specification as to "A method of treating a host having hyperlipidemia comprising administering to the host an effective amount of a compound having the formula..." is limited to agents of formula I and in table 2 the dried leaf powder of hypoestes rosea shrub, containing 0.1% hypoestoxide. Specific examples of formula I include wherein R=H or acetyl. The stereochemistry of the chiral centers of the epoxides are not defined.

The specification suggests the use of hypoestoxide in combination with other active ingredients in combination therapy.

(4) Working Examples:

The applicant provides two working examples in tables 1 and 2.

Table 1 describes the treatment of a single 2-year-old female beagle dog at a dose of 30mg/kg, once daily for seven days. The blood cholesterol and triglyceride levels were obtained at days 1, 3, 7 and 14 respectively. While table 1 uses only one subject it includes 5 data points that seem to indicate a statistically significant change in the cholesterol and triglycerides as measured for the beagle.

Table 2 describes the treatment of a single human via oral ingestion of a 1g capsule of dried leaf powder of *hypoestes rosea* shrub (parent plant of hypoestoxide),

taken once daily for one year as a dietary supplement. Table 2 only includes two data points at –1 (assumed before treatment) and 1 (assumed one year later). The examiner respectfully points out that it is generally accepted in the art that at least three data points are necessary to achieve and show statistical significance. As such the examiner has included a statistical analysis (based upon Quantitative Chemical Analysis, 3rd edition, 1991,pp 49-53) of the data points provided including the determination of the mean, standard deviation and student t-test at 95% confidence level. The results are as follows for the data from Table 2:

Cholesterol (mg/dl):

mean=210.5

standard deviation=+/-6.364

student t-test (95% confidence level)=210.5+/-57.18

Triglycerides (mg/dl):

mean=99.5

standard deviation=+/-4.95

student t-test (95% confidence level)=99.5+/-40.38

The examiner respectfully points out that the two data points when the standard deviation is taken into account significantly overlap thus indicating that the data is insufficient to indicate a statistical difference. As such the data cannot be used as evidence that the changes in the levels of cholesterol and triglycerides indicate a

therapeutic change. This is further exacerbated by the fact that there is only one subject (though the title for table 2 uses the term humans) for which data is presented.

The examiner also respectfully notes that in the single human study dried leaf powder of the hypoestes rosea shrub is utilized in stead of pure hypestoxide as was utilized in the beagle data. While the applicant indicates that hypoestoxide is present in the dried leave product at 0.1% it is understood that other compounds are also present in the dried leave product that could be accounting any variety of effects.

(5) State/predictability of the Art:

The state of the art regarding "A method of treating a host having hyperlipidemia comprising administering to the host an effective amount of a compound having the formula..." is high.

(6) The Quantity of Experimentation Necessary:

The instant claims read on "A method of treating a host having hyperlipidemia comprising administering to the host an effective amount of a compound having the formula...". Applicant fails to provide information sufficient to practice the claimed invention, absent undue experimentation (especially in humans where the applicants present only one test subject and two data points that show no statistically significant difference and further are not the pure compound hypoestoxide itself but a dried leaf powder containing hypoestoxide at 0.1% among other compounds). Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in

return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Accordingly the claims are evaluated as being drawn to a method of treating a dog having hyperlipedemia comprising administering to the dog an effective amount of a compound having the formula indicated in claim 1 wherein R=H and acetyl.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 4-10 and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ojo-Amaize et al. (US Patent No. 5801193), in view of Cybulsky et al. (Endothelial expression of a Mononuclear Adhesion Molecule During Atherogenesis, Science, 1991, vol. 251, pp 788-791) and further in view of Robbins Pathological Basis of Disease (5^{th} edition, 1994, pp. 473-483).

Ojo-Amaize et al. teach, in col. 1 line 40 to col. 2 line 30, hypoestoxide compounds of formula I and formula IV (encompassing the currently claimed compounds) effective as immunosuppressive agents. In col. 12 lines 20-45, Ojo-Maize et al. teach that the compounds of formula I and formula IV have effectiveness as immunosuppresive and anti-inflammatory agents as demonstrated by their activity in suppressing pro-inflammatory cytokines (such as TNFa, IL1b, IL6).

Ojo-Amaize et al. does not teach a method of treating a host having hyperlipidemia via administration of the compounds of formula I and formula IV.

Cybulsky et al. teach on page 790, immunohistochemical staining for mononuclear leukocyte-selective adhesion of hypercholesteremic rabbits (and Watanabe heritable hyperlipidemic rabbits) showed localized staining of the endothelium covering foam cell-rich aortic intimal lesions at various stages of their development. These stainings indicate endothelial activation in the setting of

atherosclerosis (i.e. inflammatory mononuclear leukocyte adhesion markers) are present at sites of foam-cell aortic lesions in hypercholesteremic and/or hyperlipidemic without additional pro-inflammatory factors.

Robbins teaches, on page 474, that the four most significant factors relating to the development of atherosclerosis are (1) hyperlipidemia (2) hypertension (3) cigarette smoking and (4) diabetes. On page 480, Robbins teaches that endothelial dysfunction is an important factor in the pathology of athersclerosis and that the three most important manifestations of these dysfunctions include: increased endothelial permeability, increased monocyte adhesion and increased endothelial cell replication; all of these are early events in experimental hypercholesterolemia. One postulated common pathway to injury is the activation of the NF-kB transcription factors (known pro-inflammatory factors). On pages 480-481, Robbins discloses that after adherence to the endothelium monocytes emigrate into the intima and subsequently accumulate low-density lipoprotein (LDL). Macrophages also accumulate. It is noted that macrophages are intimately involved in inflammatory responses and thus it is likely that they play a role in the progression of atherosclerotic lesions due to their production of IL1 and TNF as well as their association with chemo tactic factor for leukocytes.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the claimed compounds in methods of treating hyperlipidemia in a host as the compounds have been previously shown by Ojo-Amaize to act as anti-inflammatories via their suppression pro-inflammatory cytokines (such as TNFa, IL1b, IL6) and both Cybulsky et al. and Robbins clearly show that hyperlipidemia

is shown to be associated with the adherence of monocytes at endothelium covering foam cell-rich aortic intimal lesions at various stages of their development and further that through the binding of monocytes (and subsequently macrophages) the inflammatory processes initiated aid in the progression atherosclerotic lesions. One would be motivated to utilize the claimed compounds in order to treat hyperlipidemia as their already noted anti-inflammatory activities would aid in the alleviation of the inflammation associated with hyperlipidemia and subsequent progression of atherosclerotic lesions. One would have a reasonable expectation of success as the compounds are known anti-inflammatories and atherosclerosis is associated with inflammation and hyperlipidemia as detailed above.

The examiner respectfully points out the following from MPEP 2144.06: "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re* Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leonard M. Williams whose telephone number is 571-272-0685. The examiner can normally be reached on MF 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LMW

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER